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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,295	09/09/2002	Menachem Rubinstein	RUBINSTEIN=7	2828

1444 7590 04/02/2008

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EXAMINER	
CHANDRA, GYAN	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
04/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/070,295	RUBINSTEIN ET AL.	
	Examiner	Art Unit	
	GYAN CHANDRA	1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 February 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *5,9,11,12 and 15-18*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continued sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Robert Landsman/
Primary Examiner, Art Unit 1647

Continuation of 11 does not place the application in condition for allowance because:

Applicant's Response and Menachem's declaration to Final Rejection filed on 2/19/08 have been entered.

Claim Rejections - 35 USC § 112-enablement
The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 9, 11, 12 and 15-18 stand rejected under 35 U.S.C. 112, first paragraph-enablement for the reasons of record on pages 2-3 of the Office Action mailed on 11/2/2007.

Claims 5, 9, 11, 12 and 15-18 are drawn to a method for inhibiting angiogenesis in mammals comprising administering to a subject a pharmaceutical composition comprising (i) leptin, (ii) a leptin fragment, (iii) a leptin homolog having 90% sequence identity with sequence of leptin, or (iv) a derivative of leptin or leptin homolog which has the activity of leptin, and optionally, an inhibitor of angiogenesis in a suitable dosage, (v) wherein angiogenesis inhibitor is a VEGF inhibitor, (vi) wherein the derivative said derivative has one or more chemical moieties attached to leptin, (vii) wherein said chemical moieties are water soluble polymers, and wherein said polymers are polyethylene glycol. Applicants argue (page 2 of Response) that the animal model used in the instant invention (-ob/-ob mouse) is a customary way to establish a protein function. They reiterated their arguments that the addition of leptin to a leptin-deficient (ob/ob) mouse results in angiopoietin 2 and inhibition of angiogenesis in adipose tissue. Applicants argue that the reference Cao teaches leptin induces angiogenesis by measuring (i) capillary growth in the corneal model, and (ii) fenestration, and argue that the fenestration is different than capillary growth. Thus, appicants argue that Cao does not teach increase in capillary in adipose tissue. In support, Applicants provide Menachem's declaration and the reference Hanahan (Science, 277, 48-50, 1997).

Applicants arguments have been fully considered but they are not persuasive because the instant rejection is not based on the issue that the -ob/-ob KO mouse is not a proper model to study a gene function. The instant rejection is under 35 U.S.C. 112, first paragraph-enablement and as presented in the previous Office Action of 11/2/2007, the specification only teaches an -ob/-ob mouse where leptin inhibits angiogenesis. Further, the features upon which applicant relies (i.e., a method for inhibiting angiogenesis in -ob/-ob mouse) are not recited in the rejected claim(s). Cao et al teach that leptin induces angiogenesis (new blood vessels fenestration) in normal except in leptin deficient ob/ob mice (see abstract). Cao et al teach that wild type mouse have more capillaries that ob/ob mouse (Fig 3 and page 6392 right column). Further, the limitation "angiogenesis in adipose tissue" appears only in claim 18 and therefore, applicants arguments are not persuasive for claims 5, 9, 11,12 and 15-17. And, since the product of the prior art is identical to that required by the claims, the method will inherently lead to the same effect. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). It is well established in the art that leptin is an inducer of angiogenesis in normal mammal (IDS, Sierra-Honigmann et al, 1998; previously presented, Bouloumie et al., 1998 and previously presented, Cao et al. Proc. Natl. Acad. Sci. 98:6390-6395, 2001). Therefore, the effect of leptin on angiogenesis inhibition appears to be limited to ob/ob mice only. Applicants only argue the reference Cao but they do not argue the references Sierra-Hongamann and Boulooumie et al which support the state of art.The reference Hanahan teaches a pathway of cell proliferation and angiogenesis using VEGF and other signaling molecules (e.g., ang1 or ang2). But the reference Hanahan does not establish that leptin does not promote angiogenesis in normal animal.

The declaration of Menachem states (i) that a knockout mouse is well accepted model to study a gene function and (ii) the reference Cao does not teach or suggest that leptin induces capillary growth in adipose tissue.

Menachem's declaration that a knockout mouse is well accepted model for studying a gene function is persuasive. However, the claims are not directed to leptin function in a –ob/-ob mouse. The instant claims are directed to "a method for inhibiting angiogenesis in mammals" and the art has established that leptin is an inducer of angiogenesis in normal mammal (IDS, Sierra-Honigmann et al, 1998; previously presented, Bouloumie et al., 1998 and previously presented, Cao et al. Proc. Natl. Acad. Sci. 98:6390-6395, 2001). Further, the reference Cao et al teaches that leptin (10ng/mL) clearly induces angiogenesis as evidenced by cornea model (Fig. 1). Regarding Menachem's declaration that Cao does not teach or suggest that leptin induces capillary growth in adipose tissue is not persuasive because Cao et al teach that the endothelial growth response to leptin is dose dependent (6391, Results, capillary endothelial cell growth and Fig. 1e). Cao et al teach that wild type mouse have more capillaries that ob/ob mouse (Fig 3 and page 6392 right column). And, since the product of the prior art is identical to that required by the claims, the method will inherently lead to the same effect. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Thus, since the product of the prior art has the same chemical structure as that described in the specification, it can be assumed that the product will inherently perform the claimed process. (See MPEP 2112.02). It is noted that Menachem is a co-inventor in this application. Further, it is noted that while the declaration Menachem discusses findings in terms of "-ob/-ob mouse", no data regarding inhibition of angiogenesis by administering leptin in a normal mouse is disclosed, making it difficult for the Examiner independently to draw conclusions. Also, no published work of other researchers showing leptin's inhibitory effect on angiogenesis in a normal mouse has been cited. Based on consideration of the totality of the evidence, it is proper to maintain the rejections.

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18 March 2008
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